IgE-mediated hypersensitivity to cephalosporins: Cross-reactivity and tolerability of penicillins, monobactams, and carbapenems

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Background: There have been few studies regarding the cross-reactivity and tolerability of penicillins, aztreonam, and carbapenems in large samples of subjects with cephalosporin allergy.

Objective: We sought to evaluate the possibility of using penicillins, monobactams, and carbapenems in subjects with cephalosporin allergy who especially require them.

Methods: We conducted a prospective study of 98 consecutive subjects who had 106 immediate reactions (mostly anaphylactic shock) to cephalosporins and had positive skin test results for these drugs. To assess the cross-reactivity with penicillins, monobactams, and carbapenems and the tolerability of such alternative β-lactams, all subjects underwent skin tests and serum-specific IgE assays with penicillin reagents, as well as skin tests with aztreonam, imipenem/cilastatin, and meropenem. Subjects with negative test results were challenged with meropenem, imipenem/cilastatin, aztreonam, and amoxicillin.

Results: Positive allergologic test results to penicillins were displayed by 25 (25.5%) subjects, including 1 with positive results to all reagents tested and another with a positive result to aztreonam. Another subject had positive results to both ceftazidime and aztreonam. A reaction to cephalosporins with side-chain structures similar or identical to those of penicillins was a significant predictor of cross-reactivity because of an increased 3-fold risk of positive results on allergologic tests with penicillin determinants. Challenges with alternative β-lactams were tolerated, with the exception of 1 urticarial reaction to imipenem/cilastatin.

Conclusions: About 25% of subjects with cephalosporin allergy had positive results to penicillins, 3.1% to aztreonam, 2% to imipenem/cilastatin, and 1% to meropenem. In those who especially require alternative β-lactams, pretreatment skin tests are advisable because negative results indicate tolerability of the β-lactam concerned. (J Allergy Clin Immunol 2010;126:994-9.)

Key words: *Aztreonam, carbapenems, cephalosporin allergy, cross-reactivity, penicillins, skin tests, tolerability*

Cephalosporins and penicillins are the most widely used antibiotics for the treatment of common infections[1-3]; they are the 2 main classes of β-lactam antibiotics. Each possesses a 4-member β-lactam ring, but the 5-member thiazolidine ring of penicillins is replaced by the 6-member dihydrothiazine ring in the cephalosporin nucleus. Monobactams and carbapenems are 2 other classes of β-lactams.[4] Monobactams contain a monocyclic ring structure, whereas carbapenems have a bicyclic nucleus comprised of a β-lactam ring with an associated 5-membered ring. Like penicillins, cephalosporins can cause immediate allergic reactions that are induced by an IgE-mediated pathogenic mechanism, occur within the first hour after the last drug administration, and are manifested as urticaria, angioedema, rhinitis, bronchospasm, and anaphylaxis.[5,6] Skin tests for parent cephalosporins are useful tools for evaluating subjects with immediate reactions to these β-lactams.[7-12] With regard to *in vitro* tests, except for cefaclor, assays of serum specific IgE are not commercially available and thus are not routinely used.[6]

A number of studies have evaluated allergic cross-reactivity with cephalosporins in large samples of subjects with well-demonstrated IgE-mediated hypersensitivity to penicillins.[13-15] In these studies[13-15] subjects displaying negative results on cephalosporin skin tests underwent challenges with the cephalosporins concerned and tolerated them.

Other studies have assessed the cross-reactivity and tolerability of a monobactam (aztreonam)[16-19] and carbapenems[20-23] in subjects with IgE-mediated hypersensitivity to β-lactams, mainly penicillins, by successfully administering these alternative β-lactams to such subjects with negative results on skin tests. However, studies concerning the tolerability of aztreonam and carbapenems in subjects with IgE-mediated hypersensitivity to cephalosporins are lacking, with the exception of the study by Moss,[16] which demonstrated the tolerability of aztreonam in 4 patients with cystic fibrosis allergic to ceftazidime.

On the other hand, some studies have evaluated subjects with cephalosporin allergy to assess cross-reactivity with penicillins on the basis of positive results on either or both skin tests and specific IgE assays,[9,10,12,24-26] showing a rate of cross-reactivity ranging from 8.3% (2/24 subjects)[10] to 50% (6/12).[24] In these studies,[9,10,12,24-26] however, subjects with negative results on allergologic tests with penicillin reagents did not undergo penicillin

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challenges, with the exception of the study by Antunez et al,[10] in which 22 subjects with cephalosporin allergy who had negative results to penicillin determinants underwent benzylpenicillin challenges and tolerated them.

We conducted a prospective study to evaluate the possibility of giving penicillins, monobactams, and carbapenems to patients with documented cephalosporin allergy who especially require these treatments. To evaluate this possibility, a large group of well-characterized subjects with cephalosporin allergy was evaluated by using skin tests and serum specific IgE assays with penicillin reagents, as well as by using skin tests with aztreonam, imipenem/cilastatin, and meropenem to assess cross-reactivity and its potential determinants. Moreover, subjects with negative results on allergologic tests were challenged with meropenem, imipenem/cilastatin, aztreonam, and amoxicillin to ascertain whether negative results could be a reliable indicator of the tolerability of these β-lactams.

METHODS

Patient selection

Subjects were recruited from a large outpatient population with a history of immediate reactions to at least 1 cephalosporin. To be included in the study, a subject must have experienced a positive skin test result to the responsible cephalosporin. An indication for treatment with β-lactams other than cephalosporins was not a criterion of inclusion. We used skin tests to evaluate sensitization to aztreonam and carbapenems (imipenem/cilastatin and meropenem). In the event of negative results to penicillin reagents, we administered amoxicillin to consenting patients, whereas we administered the β-lactams concerned to subjects with negative results on skin tests with aztreonam, imipenem/cilastatin, and meropenem. Exclusion criteria were pregnancy, use of β-blockers, and severe cardiovascular, renal, or respiratory compromise. Before the study, all subjects received information about possible risks of skin and challenge tests, and we obtained written informed consent from each patient or the parents of those less than 18 years of age. The respective institutional review boards approved the protocol.

TABLE I. Clinical data of the 98 subjects with cephalosporin allergy

	No. of patients (%)
Age	44.5 (20.8)*
Female sex	68 (69.4)
Time since last cephalosporin reaction†	5.5 (1-300) [2, 18]‡
Family history of allergic diseases	38 (38.8)
Personal history of allergic diseases	32 (32.6)
Culprit drugs	No. of reactions§ (%)
Ceftriaxone	53 (49.5)
Ceftazidime	11 (10.3)
Cefaclor	11 (10.3)
Cefotaxime	11 (10.3)
Cefuroxime	5 (4.7)
Cephalexin	3 (2.8)
Cefazolin	3 (2.8)
Cefatrizine	3 (2.8)
Cephalothin	2 (1.9)
Cefodizime	2 (1.9)
Cefoperazone	1 (0.9)
Cefamandole	1 (0.9)
Aztreonam	1 (0.9)
Manifestations	No. of reactions§ (%)
Anaphylactic shock‖	84 (78.5)
Urticaria and angioedema	13 (12.1)
Urticaria	9 (8.4)
Erythema	1 (0.9)

*The first number refers to the mean age of the 98 patients expressed in years. The SD is shown in parentheses.
†Time elapsed between the last cephalosporin reaction and current allergologic testing.
‡The first number refers to the median value expressed in months. The range is shown in parentheses, and the 25th and 75th percentiles are shown in brackets.
§The total number of reactions is 107.
‖Diagnosed according to the clinical criteria proposed by Sampson et al.[31]

Prick and intradermal skin tests

We performed skin testing on 3 different days, as previously described.[9,12] On the first day, we performed skin prick and intradermal tests using penicilloyl-polylysine (Allergopharma, Reinbeck, Germany), minor determinant mixture (Allergopharma), and benzylpenicillin (Pharmacia, Milan, Italy). The final concentrations were, respectively, 5×10^{-5} mmol/L, 2×10^{-2} mmol/L, and 10,000 IU/mL. Because Allergopharma ceased production of penicillin reagents, from July 2005 we used those from Diater S.A. (Madrid, Spain): penicilloyl-polylysine (final concentration, 1.07×10^{-2} mmol/L) and minor determinant mixture (benzylpenicillin, sodium benzylpenicilloate, and benzylpenicilloic acid; final concentration, 1.5 mmol/L).

On the second day, we used ampicillin and amoxicillin at concentrations of 1 and 20 mg/mL after dilution in 0.9% NaCl.

On the third day, we used the responsible cephalosporins (Table I) at a concentration of 2 mg/mL, meropenem at 1 mg/mL, imipenem/cilastatin at 0.5 mg/mL for each component, and aztreonam at 2 mg/mL.

We diluted all reagents with 0.9% NaCl no more than 2 hours before administration. For injectable cephalosporins, we used the intravenous form under sterile conditions, whereas for noninjectable cephalosporins, we prepared a solution, as previously described.[9]

We performed positive controls for skin prick and intradermal tests with histamine (at 10 and 1 mg/mL, respectively). As a negative control for skin prick and intradermal tests, we used 0.9% NaCl.

All reagents were initially tested on volar forearm skin by using the prick method; results were considered positive when a wheal larger than 3 mm in diameter with surrounding erythema was present 20 minutes later. When skin prick test results were negative, 0.02 mL of the reagent solution was injected intradermally on volar forearm skin. Readings were made 20 minutes after injections. Results were considered positive when an increase larger than 3 mm in the initial wheal diameter was accompanied by erythema.[9,27] A wheal without erythema was considered an equivocal result.

The concentrations used for cephalosporins, aztreonam, meropenem, and imipenem/cilastatin had proved to be nonirritating in previous studies.[9,12,17,20-23,28] Specifically, the concentration of 2 mg/mL used for cephalosporins is the one recommended by the European guidelines.[8,29]

Detection of specific IgEs in serum

We collected blood samples when patients were evaluated and stored the sera at −20°C until they were assayed. We performed assays for serum specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, and cefaclor (CAP-FEIA), according to the manufacturer's instructions, with UniCAP (Phadia, Uppsala, Sweden) in all 106 subjects. We considered a positive result (ie, detectable specific IgE antibodies) to be a value of 0.35 kU/L or greater.

β-Lactam challenges (test dosing)

We also performed controlled administrations of therapeutic doses of meropenem (1 g administered intravenously), imipenem/cilastatin (500 mg of each component administered intramuscularly), aztreonam (1 g administered intramuscularly), and amoxicillin (1 g administered orally), each on a different day, in subjects who had negative results in the allergologic tests. We administered an initial dose of one hundredth of the therapeutic dose. In cases with negative results, 1 hour later, we administered a dose of one tenth of the therapeutic dose, and if the result was again negative, after another hour, we administered a full dose.

After the first 30 tests with each β-lactam, we modified this workup, administering an initial dose of one tenth of the therapeutic dose, and if the result was negative, 1 hour later, we administered a full dose.

We carefully monitored each patient during challenges until 3 hours after the administration of the full dose; complete equipment for cardiopulmonary resuscitation was immediately available.

We did not administer amoxicillin to subjects with positive allergologic test results for penicillin reagents; likewise, we did not administer the β-lactam concerned to patients with positive skin test responses to meropenem, imipenem/cilastatin, and aztreonam because such positivity could indicate a sensitization.

Statistical analysis

We collected the data prospectively and analyzed them with Stata software (StataCorp, College Station, Tex). Our goal was to assess the cross-reactivity with alternative β-lactams and its potential determinants in patients with documented cephalosporin allergy.

We have presented the frequency of positive results as a percentage and exact 95% CI.[30] We have compared the group of patients who were cross-reactive with those who were not. Age is reported as means ± SDs and the time interval between the last adverse reaction and testing as medians and ranges. We have compared these continuous variables by using a Mann-Whitney *U* test. We have presented categorical data as the number of cases and percentages and compared them using the χ^2 and Fisher exact tests. A *P* value of .05 or less indicates statistical significance. We have calculated the relative risk ratios and the corresponding 95% CIs to assess the determinants significantly associated with cross-reactivity.

RESULTS

We examined 98 subjects (68 female and 30 male subjects) who ranged in age from 13 to 90 years (mean age, 44.5 ± 21 years) and had a well-demonstrated, IgE-mediated hypersensitivity to cephalosporins. These subjects constituted 71% of an outpatient population of 138 adults recruited prospectively between January 2000 and December 2008 in the Allergy Units of C.I. Columbus and Oasi Maria S.S. because they had a history of immediate reactions to cephalosporins. None of the 98 subjects had a history of hypersensitivity reactions to penicillins; 42 of them were reported in a previous study of ours.[9] We performed our workup with intervals ranging from 1 to 300 months (median, 5.5 months) after the most recent adverse reaction. None of these cases had any exclusion criteria.

The clinical data and allergologic test results are summarized in Tables I and II. The compounds that most frequently caused allergic reactions were ceftriaxone, ceftazidime, cefaclor, and cefotaxime (Table I).

Our 98 patients had experienced a total of 106 immediate reactions to cephalosporins and 1 to aztreonam. More than 75% of patients had experienced an anaphylactic reaction, which was diagnosed according to the clinical criteria proposed by Sampson et al.[31] Eighty-nine subjects had experienced only 1 reaction to a cephalosporin, 6 subjects had 2 reactions to the same cephalosporin (4 to ceftriaxone, 1 to cefaclor, and 1 to cefatrizine), and 2 subjects experienced 2 distinct reactions to different cephalosporins (1 to both ceftazidime and cefotaxime and another to both cefuroxime axetil and cefotaxime), whereas in 1 case reactions to different β-lactams in separate episodes occurred (Table III, patient 26).

All 98 subjects had positive skin test results to the responsible cephalosporins tested (Table II); 11 (11.2% [95% CI, 6.4% to 19%]) of them also had positive results to penicillin reagents. Among the latter subjects, 5 had positive responses to either ampicillin, amoxicillin, or both, only at the concentration of 20 mg/mL (Table III, patients 5, 6, and 9-11).

TABLE II. Allergologic test results of the 98 subjects with cephalosporin allergy

	No. of patients (%)
Positive skin test results to β-lactams	
Penicilloyl-polylysine	5 (5.1)
Minor determinant mixture	5 (5.1)
Benzylpenicillin	7 (7.1)
Ampicillin	8 (8.2)
Amoxicillin	9 (9.2)
Ceftriaxone	49 (50)
Ceftazidime	11 (11.2)
Cefotaxime	11 (11.2)
Cefaclor	10 (10.2)
Cefuroxime	5 (5.1)
Cefazolin	3 (3.1)
Cephalexin	3 (3.1)
Cefatrizine	1 (1)
Cephalothin	1 (1)
Cefodizime	1 (1)
Cefamandole	1 (1)
Cefoperazone	1 (1)
Cefonicid	1 (1)
Aztreonam	3 (3.1)
Imipenem	1 (1)
Meropenem	1 (1)
Positive specific IgE assay results	
Penicilloyl G	12 (12.2)
Penicilloyl V	13 (13.3)
Ampicilloyl	10 (10.2)
Amoxicilloyl	3 (3.1)
Cefaclor	10 (10.2)

With regard to skin testing with β-lactams other than penicillins and cephalosporins, 1 (1% [95% CI, 0.2% to 5.5%]) subject had positive results to both meropenem and imipenem/cilastatin, as well as to all the other reagents tested (Table III, patient 6), and 3 (3.1% [95% CI, 1.1% to 8.6%]) subjects had positive results to aztreonam: the one just mentioned (Table III, patient 6), another with positive allergologic test results also to cefodizime and penicillin V (Table III, patient 20), and the last with positive skin test results to both aztreonam and ceftazidime, the responsible drugs (Table III, patient 26).

As far as *in vitro* assays are concerned, 21 (21.5% [95% CI, 14.5% to 30.6%]) of the patients had positive results: 11 to only penicillin reagents, 5 to only cefaclor (the responsible cephalosporin), and 5 (one of whom had reacted to cefaclor) to both the penicillin reagents and cefaclor.

When considering the results of both skin tests and specific IgE assays with the penicillin reagents, 25 (25.5% [95% CI, 17.9% to 34.5%]) subjects had positive results to these reagents (Table III).

Challenges with meropenem (in 97 subjects), imipenem/cilastatin (in 97 subjects), aztreonam (in 95 subjects), and amoxicillin (in 73 subjects) were well tolerated with the exception of 1 subject, who experienced a mild urticarial eruption 30 minutes after the full dose of imipenem/cilastatin (Table III, patient 9).

Of our total of 98 patients, 25 (25.5%) had positive responses to penicillin reagents, 3 (3.1%) to aztreonam, 2 (2% [95% CI, 0.6% to 7.1%]) to imipenem/cilastatin, and 1 (1%) to meropenem (Table III); 72 (73.5% [95% CI, 63.9% to 81.2%]) subjects had

TABLE III. Clinical data and allergologic test results of the 34 subjects with cephalosporin allergy with positive results to β-lactams other than cephalosporins on skin tests, specific IgE assays, or both

					CAP-FEIA					Skin tests								
Patient no.	Sex	Age (y)	Drug involved	Type of reaction	PG	PV	AMy	AXy	CE	PPL	MDM	BP	AM	AX	Culprit*	AZ	IM	ME
1	F	50	Cephalexin	AS	1.1	1.36	1.7	−	−	+	+	+	+ p 1	+ p 1	+	−	−	−
2	M	28	Cephalothin	AS	0.41	−	−	−	−	+	+	+	+ i 1	+ i 1	+	−	−	−
3	F	63	Cefuroxime	AS	−	−	−	−	−	+	−	−	−	−	+	−	−	−
4	F	61	Ceftriaxone	AS	−	−	−	−	−	+	+	+	−	−	+	−	−	−
5	F	38	Ceftriaxone	AS	−	−	−	−	−	−	−	+	+ i 20	+ i 20	+	−	−	−
6	M	44	Cefamandole	AS	−	−	−	−	−	+	+	+	+ i 1	+ i 20	+	+	+	+
7	F	45	Cefatrizine	AS	−	−	−	−	−	−	−	−	−	+ i 1	+	−	−	−
8	F	13	Cefaclor	AS	−	−	−	−	+	−	−	+	+ i 1	+ i 1	+	−	−	−
9†	F	13	Cefaclor	AS	−	−	−	−	−	−	−	+	+ i 20	+ i 1	+	−	−	−
10	F	61	Ceftriaxone	AS	−	−	−	−	−	−	+	−	+ i 20	+ i 1	+	−	−	−
11	F	14	Cefaclor/cefaclor	U/AS	−	−	−	−	−	−	−	−	+ i 20	+ i 20	+	−	−	−
12	F	35	Ceftazidime	AS	0.63	0.56	−	−	−	−	−	−	−	−	+	−	−	−
13	F	46	Cefaclor	AS	−	−	2.68	−	−	−	−	−	−	−	+	−	−	−
14	M	24	Cephalothin	UA	1.28	1.49	1.39	0.68	−	−	−	−	−	−	+	−	−	−
15	F	47	Ceftriaxone/ceftriaxone	U/AS	8.2	9.27	2.57	−	−	−	−	−	−	−	+	−	−	−
16	M	79	Ceftriaxone	AS	0.38	0.63	−	−	−	−	−	−	−	−	+	−	−	−
17	F	48	Ceftazidime	AS	−	0.4	−	−	−	−	−	−	−	−	+	−	−	−
18	M	49	Ceftriaxone	UA	0.81	0.76	1.19	−	0.47	−	−	−	−	−	+	−	−	−
19	M	59	Ceftriaxone	U	0.47	−	−	−	−	−	−	−	−	−	+	−	−	−
20	F	78	Cefodizime	AS	−	0.49	−	−	−	−	−	−	−	−	+	+	−	−
21	F	25	Cefaclor	UA	4.49	14.9	0.36	−	2.5	−	−	−	−	−	+	−	−	−
22	F	59	Cefuroxime axetil	UA	−	1.16	−	−	−	−	−	−	−	−	+	−	−	−
23	F	58	Ceftriaxone	AS	0.38	1.67	0.4	−	0.56	−	−	−	−	−	+	−	−	−
24	M	67	Ceftriaxone	AS	0.67	2.39	1.57	0.68	0.47	−	−	−	−	−	+	−	−	−
25	F	51	Ceftriaxone	AS	1.62	2.52	0.96	1.02	0.67	−	−	−	−	−	+	−	−	−
26	M	50	Ceftazidime/aztreonam	AS/AS	−	−	−	−	−	−	−	−	−	−	+/+	+	−	−

AM, Ampicillin; *AMy*, ampicilloyl; *AS*, anaphylactic shock; *AX*, amoxicillin; *AXy*, amoxicilloyl; *AZ*, aztreonam; *BP*, benzylpenicillin; *CE*, cefaclor; *F*, female; *i 1*, intradermal test at 1 mg/mL, *i 20*, intradermal test at 20 mg/mL; *IM*, imipenem/cilastatin; *M*, male; *MDM*, minor determinant mixture; *ME*, meropenem; *p 1*, skin prick test at 1 mg/mL; *PG*, penicilloyl G; *PPL*, penicilloyl-polylysine; *PV*, penicilloyl V; *U*, urticaria; *UA*, urticaria and angioedema.

*Tested at concentrations of up to 2 mg/mL.

†This patient experienced an urticarial eruption after imipenem challenge.

negative responses in allergologic tests, including challenges, with β-lactams other than cephalosporins.

With regard to the cross-reactivity with penicillins, we found no significant difference in sex, age, time interval between the last adverse reaction and allergologic examination, or clinical manifestations of cephalosporin allergy between patients who presented positive results in allergologic tests for penicillin determinants and those who did not. However, we observed positive results on allergologic tests for penicillin determinants in 10 (55.5% [95% CI, 33.5% to 75.5%]) of 18 subjects who had reacted to cephalosporins that share similar (cephalothin or cefamandole) or identical (cefaclor, cephalexin, or cefatrizine) side chains with penicillins versus 15 (18.7% [95% CI, 11.7% to 28.7%]) of 80 subjects who reacted to cephalosporins (ceftriaxone, ceftazidime, cefotaxime, cefuroxime, cefazolin, cefodizime, cefoperazone, or cefonicid) that have side chains different from those of penicillins ($P < .01$, Fisher exact test). After reacting to a cephalosporin that shares a similar or identical side chain with penicillins, the estimated relative risk ratio of cross-reacting with at least 1 penicillin was 3.0 (95% CI, 1.6% to 5.5%).

DISCUSSION

IgE-mediated reactions to cephalosporins occur because of sensitization to determinants shared with other β-lactams or to unique cephalosporin haptens.[32-34] Therefore in subjects with hypersensitivity reactions to cephalosporins, physicians should use responsible cephalosporins in allergologic tests in addition to the classic penicillin reagents.[8,29,35] The rate of positive responses to the penicillin reagents observed in the present study (25.5% [25/98] of subjects) falls within the range of such rates found in the aforementioned studies,[9,10,12,24-26] which evaluated subjects with cephalosporin allergy to assess cross-reactivity with penicillins on the basis of positive results on either or both skin tests and specific IgE assays. Having reacted to cephalosporins with side-chain structures similar or identical to those of penicillins was a significant predictor of cross-reactivity because it increased 3-fold the risk of having positive results on allergologic tests with penicillin determinants. However, 15 of the 25 subjects with positive results to penicillins had reacted to cephalosporins with side-chain structures different from those of penicillins. Therefore our results demonstrate that the risk of positive results on allergologic tests with penicillin reagents is not related only to the structural similarities between the side-chain determinants of cephalosporins and penicillins,[33,36] which confirms the results of a study of ours concerning 128 subjects with penicillin allergy,[15] 5 (3.9%) of whom had positive skin test results to cefuroxime, ceftriaxone, ceftazidime, or cefotaxime.

Fourteen (14.3%) patients in the present study had positive results on both skin tests with the responsible cephalosporins and

IgE assays with penicillins. However, *in vitro* cross-reactivity does not predict a clinical reaction. In effect, many patients with detectable IgE antibodies do not display such reactions.[37] For example, subjects with a selective reaction to amoxicillin and good tolerance to benzylpenicillin have some degree of IgE recognition to the latter in immunoassays, as well as in competition assays.[29,38] Nevertheless, in the present study subjects with positive results to penicillin reagents did not undergo amoxicillin challenges.

As far as β-lactams other than penicillins are concerned, the rate of positive responses to skin testing with aztreonam, imipenem/cilastatin, and meropenem was 3.1%, 1%, and 1%, respectively. Therefore such a rate with carbapenems is almost identical to that found in previous studies of ours concerning subjects with penicillin allergy.[20-23]

The only subject in the present study who had positive skin test results for imipenem/cilastatin and meropenem also had positive results to all the other reagents, including aztreonam (Table III). Therefore his IgE antibodies were probably directed against a common nuclear determinant, the β-lactam ring, which is shared by all β-lactams. With regard to the other 2 subjects who had positive skin test results for aztreonam (Table III), 1 reacted to cefodizime and the other reacted to both ceftazidime and aztreonam, which share an identical side chain. In this connection a case of sensitization to aztreonam with cross-reactivity with ceftazidime diagnosed by means of skin testing has already been reported.[39] However, none of the other 10 subjects of the present study who were allergic to ceftazidime had a positive skin test result for aztreonam. Moreover, in the aforementioned study by Moss,[16] all 4 patients with cystic fibrosis and ceftazidime allergy tolerated aztreonam, and Iglesias Cadarso et al[40] described a patient with IgE-mediated anaphylaxis to aztreonam who later tolerated ceftazidime. All this confirms that the risk of cross-reactivity is not related only to the side-chain determinants.

Challenges with meropenem, imipenem/cilastatin, aztreonam, and amoxicillin were well tolerated, with the exception of 1 subject who reacted to imipenem/cilastatin (Table III). Therefore taking into account the results of both skin tests and challenges, the rate of cross-reactivity with imipenem in the present study is 2% (2/98 subjects). In any case our data demonstrate that negative results on skin tests with β-lactams are a useful indicator of tolerability and essentially confirm the data of the studies, which addressed the clinical issue of cross-reactivity of cephalosporins with either penicillins (in 24 subjects)[10] or aztreonam (in 4 subjects)[16] from the perspective of subjects with IgE-mediated hypersensitivity to cephalosporins. The results of the present study also confirm those of the studies in which subjects with an IgE-mediated hypersensitivity to penicillins were administered cephalosporins,[13-15] aztreonam,[16-19] or carbapenems.[20-23] In all these studies,[13-23] the negative predictive value of skin tests with the alternative β-lactams was very high; in effect, there were no adverse reactions to alternative β-lactams found to have negative results on skin tests.

However, the present study has some limitations. Even though skin tests with cephalosporins have been used in numerous studies, their positive and negative predictive values are not fully established.[5] Moreover, considering that all our subjects had been treated with penicillins some time before their cephalosporin hypersensitivity reactions, we find it difficult to determine whether some subjects with cephalosporin allergy had positive responses to penicillin reagents because of cross-reactivity with cephalosporins or because of coexisting sensitivities. Finally, we did not administer full therapeutic courses after challenges with alternative β-lactams because we studied our patients for research purposes rather than for clinical indications for treatment.

In any case our data, as well as those furnished by Antunez et al,[10] provide significant clinical support to the conclusion of the Joint Task Force on Practice Parameters regarding the management of patients with histories of immediate reactions to cephalosporins who require a penicillin.[41] In accordance with such parameters, these patients should undergo penicillin skin testing. If results are negative, they can receive a penicillin; if results are positive, they should receive an alternative antibiotic or, if the latter cannot be used, undergo penicillin desensitization.

On the other hand, our data indicate a very low rate of cross-reactivity between cephalosporins and both aztreonam and carbapenems. Therefore the practice of avoiding the latter in patients with cephalosporin allergy should be reconsidered. In patients with such hypersensitivity who need carbapenem therapy, we recommend pretreatment skin tests. Considering that 1 subject in the present study reacted to the imipenem challenge even though she had a negative skin test result, graded challenges are advisable until further studies have been performed to fully establish the negative predictive value of carbapenem skin tests.

Clinical implications: Approximately 75% of subjects who are allergic to cephalosporin can tolerate penicillins, and more than 95% can tolerate aztreonam, imipenem/cilastatin, and meropenem.

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